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April 25, 1999

Michael A.Friedman, M.D.
Deputy Commissioner, HF-28
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Friedman:

On June 27, 1997, Robert M. Sayre, Ph.D., wrote you a letter titled "Need to Reform Indoor Tanning Industry" and I would like to comment on some points he made. It is my understanding that his letter provided impetus for the issuance of the Food and Drug Administration's recent Advanced Notice of Proposed Rulemaking (ANPRM) that was published in the Federal Register on February 9, 1999 as Docket Number 98N-1170. The decision was made to answer his letter while helping to prepare a response to the ANPRM and it became obvious that a number of the "reforms" that Dr. Sayre called for in his letter were not supported by the facts.

The first "reform" item Dr. Sayre addressed was regarding the "accumulation of exposure from UV tanning devices" and he stated that a paper by Stern et al titled "Malignant melanoma in patients treated for psoriasis with methoxysalen (psoralen) and ultraviolet A radiation (PUVA) that was published in the *New England Journal of Medicine* (1997; 336:1041-1045) "caused me to re-examine the exposures and accumulation of exposure in UVA tanning units". It is difficult to understand how the reference cited could possibly have caused him to reach his conclusion that there is a link between PUVA therapy and a safety issue involving tanning units since Dr. Sayre was either the lead or contributing author on several papers that examined the subject of erythemal tolerance to ultraviolet radiation (UVR). He knew, or ought to have known, that there are fundamental and significant differences between PUVA and the controlled exposure to UVR provided by commercial tanning units. Therefore, in order to fully understand this issue, it is necessary to examine these differences.

In the Parrish et al paper "Photochemotherapy of Psoraisis with Oral Methoxsalen and Longwave Ultraviolet Light" that was published in the December 5, 1974 issue of the *New England Journal of Medicine*, the authors stated the following:

> "The photosensitizing property of both methoxsalen (8-methoxypsoralen) and trioxsalen (4,5', 8-trimethylpsoralen) is related to the ability of the photoexcited psoralen molecules (triplet state) to transfer the absorbed ultraviolet energy to DNA. In this photochemical reaction, psoralen covalently binds to DNA, forming monofunctional single-strand photoadducts with thymine bases and interstrand cross links (bifunctional adducts) between opposite pyrimidine base pairs. The formation of these C_4 -cyclobutane photoadducts of psoralen and pyrimidines presumably leads to inhibition of DNA synthesis. This inhibition of epidermal DNA synthesis is the rationale for the use of psoralens in the treatment of psoraisis."

98N-1170

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By increasing patients sensitivity to UVR, psoralens decrease their erythemal tolerance threshold (to UVR) and the magnitude of the photochemical reaction can be quantitated by examining the data provided by Parrish et al in this paper. When the erythemal tolerance to broad spectrum UVR is compared to PUVA, we find that PUVA decreased patients tolerance to UVR by over 80% which means there was a 5-fold or more increase in sensitivity that can be directly attributed to the psoralens administered. Furthermore, the authors statement in their paper that they were exposing their patients to "high-intensity (2.4 to 4.8 J/cm2) longwave ultraviolet light" must also be kept in mind.

Therefore, if one examines Dr. Sayre's statement that "Stern et al suggest that patients after 250 treatments seem to be at high risk (of developing melanoma)" in the context of a 5-fold or more increase in psoralen induced photosensitivity, one can see that his conclusion was not supported by the evidence presented in this paper. Furthermore, Dr. Sayre neglected to mention that the importance of the 250 session threshold was mediated by the fact that it also took from 15 to 20 years for a higher than expected number of melanoma skin cancers to develop in the patients being followed. In fact, for the first 15 years, the observed number of melanoma cases was less than expected. The average age for the patients reported on by Stern et al was 51 at enrollment time and their average age was 66 (15 years) to 71 (20 years) at the time of this study, another confounding factor to consider.

After taking into consideration the fact that psoralens "transfer the absorbed ultraviolet energy to DNA" as Parish et al clearly stated which results in a 5-fold or more increase in sensitivity to UVR and the fact that "high-intensity" levels of UVR were used in PUVA photochemotherapy, I estimate that it would be necessary for a person to tan three to four times each week in a tanning unit for 75 to 100 years to reach the equivalent cumulative irradiance levels that the PUVA patients attained in 15 to 20 years. Therefore, if one assumes that most people begin patronizing indoor tanning salons at about age twenty, it can be seen that death from a natural cause will likely occur before any (other than beneficial) effects of UVR could be observed. Furthermore, the progressive development of facultative (acquired - better known as a tan) photoprotective pigmentation (FEP3) in a controlled exposure tanning unit serves to protect DNA from UVR damage.

In summary, there are no facts to support Dr. Sayre's conclusion that the Stern et al paper provided evidence related to the accumulation of exposure from UV tanning devices since psoralens are not administered to, nor used by, clients patronizing indoor tanning salons. Indeed, the PUVA problem belongs solely and completely to the dermatology community.

Dr. Sayre also stated that "In natural sunlight it would be difficult to accumulate more than 7 or 8 MED's of UVA exposure each week or not more than 300 to 400 (MED's) a year outdoors" which is an incredible statement given his background in studying erythemal tolerance. The paper "Skin type, minimal erythema dose (MED), and sunlight acclimatiztion" that was published in 1981 in the Journal of the American Academy of Dermatology is a landmark study of erythemal tolerance and none other than Robert M. Sayre, Ph.D. was the lead author of that paper. The abstract of this paper stated that:

1. "Each skin type was shown to be statistically different from each other skin type in terms of sunburn sensitivity."

2. "During the summer, those who went outdoors were more resistant to sunburn than those who stayed indoors."

3. "In effect, acclimatization makes an individual respond to sunlight like a less sensitive skin type."

Therefore, Dr.Sayre knew, or ought to have known (unless he forgot what he wrote in 1981), that it is meaningless and misleading to talk about the erythemal tolerance threshold to UVR of an individual unless you clearly state (1) the skin phototype, and (2) the level of facultative photoprotective pigmentation that has been developed. When one looks at the increase in the erythemal tolerance threshold to UVR that occurs due to the synergistic interaction between these two factors, it is obvious that a skin phototype III with a dark tan can accommodate significantly more UVR without developing erythema than can a skin phototype I who is genetically incapable of tanning or a skin phototype II with a light tan.

I presume that Dr. Sayre wrote his letter to you in haste and did not have time to check the veracity of his statements because the alternative to this presumption is that he had other motives for writing the letter.

I am deeply involved in investigating the feasibility of utilizing UVR (especially UV-A1) in the treatment of a number of diseases. I am also a member of the Salon Advisory Panel of the International Smart Tan Network (ISTN) from which I derive no compensation and, in fact, I spend a considerable amount of my own time and money in the support of this activity. Currently, I am co-chair of the Federal Regulatory Review Committee of ISTN, a group that is formulating a response on behalf of tanning salon owners to the FDA's ANPRM. My wife owns and operates three tanning salons in Tucson, Arizona. I am actively involved in a variety of activities designed to raise the professionalism of indoor tanning salons and I wholeheartedly support the concept of utilizing education and self-regulation rather than expensive and unneccessary regulation to accomplish our goals.

As you can see, Dr. Friedman, I have sent Dr. Sayre a copy of this letter. I hope he chooses to respond to it and when he does it would be very enlightening if he would follow my example and set forth his relationship, financial and otherwise, with the dermatology community and/or the sunscreen industry. If he receives, or has received, financial remuneration from either or both of them, it could indicate a conflict of interest that must be kept in mind when examining his letter to you that, in my opinion, unfairly defames and demeans the members of the indoor tanning industry. Should he choose not to disclose or deny his relationship with the dermatology community and/or the sunscreen industry it would indicate, to a reasonable person, that he may have something to hide.

In a subsequent letter I will discuss certain other statements made by Dr. Sayre in his letter to you, especially our differing views regarding the best way to educate the American public about the risks and benefits of exposure to ultraviolet radiation.

Sincerely,

Donald L Smith

Donald L. Smith
President

CC: W. Howard Cyr, Ph.D. / ANPRM Contact / HFZ-114 / CDRH / FDA
Joseph Levy / Executive Director / International Smart Tan Network
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